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Synthesis of unsymmetrical biaryls by electroreductive cobalt-catalyzed cross-coupling of aryl halides

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Abstract—The consumable anode process allows the electrochemical cross-coupling reaction between various functionalized aromatic halides (iodides, bromides and chlorides) in the presence of cobalt halides as catalyst in a mixed solvent acetonitrile/pyridine (9:1). A great variety of unsymmetrical biaryls are obtained in moderate to excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

Unsymmetrical biaryls are an important class of organic compounds. In fact, the biaryl unit is present in several types of compounds of current interest such as natural products, polymers and molecules with medicinal importance.[1–3] So, the synthesis of unsymmetrical biaryls has been much studied over the last two decades and a number of catalytic methods devoted to the preparation of these molecules from two different monoaryl precursors have been developed.[4]

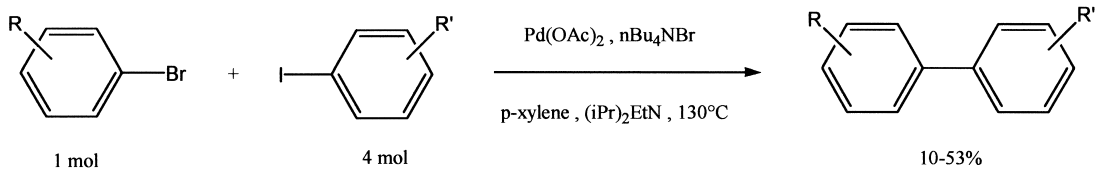
Karasch,[5,6] Negishi,[7] Stille[8] and Suzuki[9] reactions are the most classical catalytic methods used for biaryl synthesis. The preparation of organometallic intermediates such as Grignard, arylzinc and arylstannane reagents is required and biaryls are prepared by cross-coupling between the organometallic and an aryl halide in the presence of Ni or Pd complexes as catalysts. However, these methods require the use of stoichiometric amounts of organometallic precursors.

Alternatively, Ullmann conditions[10,11] allow the cross-coupling between two different aryl halides without formation of these organometallic species. Nevertheless, this method requires a stoichiometric amount of copper and high reaction temperature in the most cases. Recently, a new preparation of unsymmetrical functionalized biaryls using $Pd(OAc)_2$ as catalyst in the presence of a base has been developed (Scheme 1).[12]

This method presents some disadvantages. The first one is the use of an important excess of aryl bromide in comparison with aryl iodide (4:1), inducing difficulties in separation which decrease the isolated yields. Moreover, this process is restricted to the use of an aryl iodide and an aryl bromide. No examples were found in the literature mentioning the coupling between two aryl bromides or the synthesis of biaryls bearing electron-withdrawing groups on each aromatic ring.

Alternative simple electrochemical methods have also been used to form symmetrical biaryls, based on the electroreduction of aromatic halides in the presence of Pd[13] or Ni[14,15] catalysts.

In our laboratory, unsymmetrical biaryls have also been synthesized by electroreductive coupling between two different aryl halides catalyzed by a complex of Ni associated to 2,2′-bipyridine.[16] Nevertheless, these biaryls are substituted by an electron-donating group and an electron-withdrawing group but never by two electron-withdrawing groups. More recently, we carried out the



Scheme 1.

Keywords: biaryls; electron-withdrawing group; aryl halides; cobalt.

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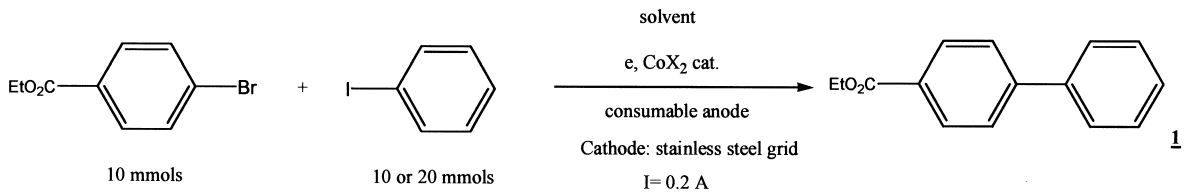


Scheme 2.

electrosynthesis of functionalized 2-arylpyridines,[17,18] 2-arylpyrimidines and 2-arylpyrazines[19] by the same catalytic process.

In a recent paper, we have shown that cobalt(I) formed by electroreduction of CoX_2 (X=Br or Cl) in dimethylformamide or acetonitrile as solvent containing pyridine as ligand undergoes fast reaction with aryl bromides or activated chlorides.[20,21] This explains the previous success in the electrosynthesis of organozinc species[22,23] catalyzed by CoX_2 in the presence of $ZnBr_2$ and with a consumable zinc anode. We also took advantage of this property to couple aryl halides with activated olefins[24] and 4-chloroquinoline derivatives.[25]

We explore in this paper the scope of this catalytic process in the cross-coupling between two different functionalized aryl halides in the mixture acetonitrile/pyridine (9:1). We have also extended the cross-coupling between a functionalized aryl bromide and 3-bromothiophene.

1. Results and discussion

1.1. Coupling between iodobenzene and ethyl 4-bromobenzoate

The coupling process was optimized from the coupling reaction between iodobenzene and ethyl 4-bromobenzoate, according to Scheme 2.

Reactions are carried out in an undivided cell fitted with various metal rods as anodes and a stainless steel grid as the cathode. To 50 ml of solvent, generally acetonitrile or dimethylformamide–pyridine (v/v=9:1), are added one equivalent of ethyl 4-bromobenzoate (the less reactive aromatic halide towards Co^I), 1 or 2 equiv. of iodobenzene (the more reactive aromatic halide towards Co^I), anhydrous cobalt chloride (0.3 equiv.) and tetrabutylammonium tetrafluoroborate (0.1 g) in order to ensure the conductivity of the electrolysis medium. Electrolyses are conducted at room temperature at a constant current intensity of 0.2 A, until 5000–6000 C are passed corresponding to total consumption of aryl halides.

The influence of various parameters was studied such as the nature of the solvent, temperature, metal of the consumable anode, ratio between aryl halides. Table 1 gives the reaction conditions and results for the reaction given in Scheme 2. The yields corresponding to the formation of Ar–Ar′, Ar–Ar and ArH are given vs. ArBr. The best results were obtained in entry 10, but in all experiments Ar′–Ar′ is also formed in great amounts by electroreductive dimerisation of Ar′I. Ar′H remains a minor product.

In a previous work, we have emphasized the fact that the amount of cobalt chloride introduced plays a major role in the overall process. Indeed, the proportion of unsymmetrical biaryl increases with cobalt chloride concentration. We have limited its quantity to 30 mol% vs. original ArBr to remain in a correct catalytic process. If only 20 mol% of cobalt chloride is introduced, the major product is Ar–Ar (49%) and Ar–Ar′ is obtained in only 40% yield.

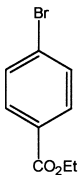
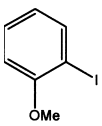
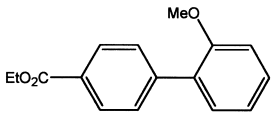
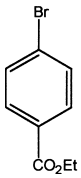
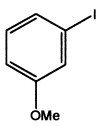
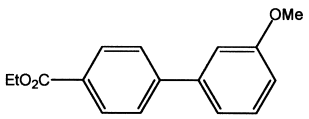
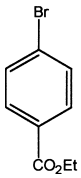
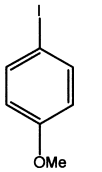
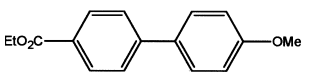
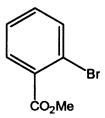
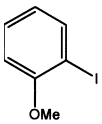
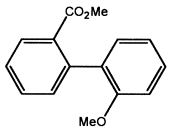
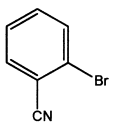
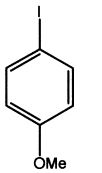
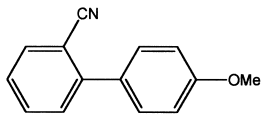
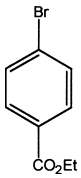
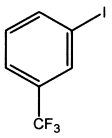
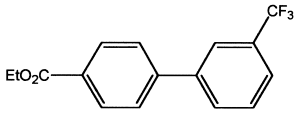
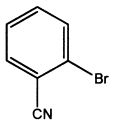
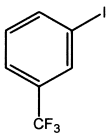
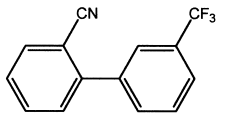
Solvent was the first parameter studied. Presence of pyridine as co-solvent and/or ligand vs. Co^I is fundamental. In the absence of pyridine (entry 2, Table 1), the homocoupling reaction becomes predominant, and biaryl Ar–Ar is formed. The proportion of pyridine in the solvent mixture is also important. If pyridine is introduced in a high proportion (entry 11, Table 1), the yield of unsymmetrical biaryl decreases. If acetonitrile is replaced by DMF (entry 3, Table 1), the electrolysis leads to the formation of ArH as the main product.

Unsymmetrical biaryl is formed even if the iron anode is

Table 1. Cross-coupling between ethyl 4-bromobenzoate and iodobenzene, influence of the reaction parameters

Entry	Solvent (v/v) [temperature]	Anode	Ratio ArBr/Ar′I	CoX_2/ArBr 30%	Conv. (%)	Ar–Ar′ yield GC (%)	Ar–Ar yield GC (%)	ArH yield GC (%)
1	Acetonitrile/pyridine (9:1) [20°C]	Iron	1:1	$CoCl_2$	100	56	39	5
2	Acetonitrile [20°C]	Iron	1:1	$CoCl_2$	53	10	42	1
3	DMF/pyridine (9:1) (20°C]	Iron	1:1	$CoCl_2$	100	8	2	90
4	Acetonitrile/pyridine (9:1) [20°C]	Zinc	1:1	$CoCl_2$	94	21	37	36
5	Acetonitrile/pyridine (9:1) [20°C]	Aluminium	1:1	$CoCl_2$	100	5	5	90
6	Acetonitrile/pyridine (9:1) [20°C]	Iron/Ni (64:36)	1:1	$CoCl_2$	47	24	12	11
7	Acetonitrile/pyridine (9:1) [50°C]	Iron	1:1	$CoCl_2$	96	48	42	6
8	Acetonitrile/pyridine (9:1) [20°C]	Iron	1:1	$CoBr_2$	100	50	44	6
9	Acetonitrile/pyridine (9:1) [20°C]	Iron	1:1	$Co(acac)_2$	100	1	0	99
10	Acetonitrile/pyridine (9:1) [20°C]	Iron	1:2	$CoCl_2$	100	75	21	4
11	Acetonitrile/pyridine (4:1) [20°C]	Iron	1:2	$CoCl_2$	96	61	25	10

Table 2. Cross-coupling between aryl bromides and aryl iodides

Entry	ArBr (10 mmol)	Ar′I (20 mmol)	Product, isolated yield (%) vs. initial ArBr	ArH yield GC (%)	ArAr yield GC (%)	Ar′–Ar′/Ar′H
1			 **85** **2**	4	11	4.8
2			 **72** **3**	3	25	7.5
3			 **88** **4**	3	9	5.2
4			 **90** **5**	2	8	1.9
5			 **81** **6**	16	3	3.4
6			 **57** (76 % GC)[a] **7**	12	12	3.8
7			 **81** [a] **8**	11	8	5.0

[a]Ar′I is introduced in excess due to his high reactivity: 30 mmol.

replaced by zinc, aluminum or iron/nickel (64:36) anodes (entries 4–6, Table 1). Nevertheless, iron leads to better yields as already described in our previous papers. However, we do not have satisfactory explanation for that behavior. Further studies are in progress in order to elucidate the role played by iron species.

Other cobalt salts have also been studied. Cobalt bromide (entry 8, Table 1) gives similar results than cobalt chloride but $Co(acac)_2$ was found inefficient towards biaryl synthesis (entry 9, Table 1). In that case, the reduction product is the only one formed.

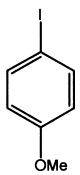
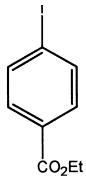
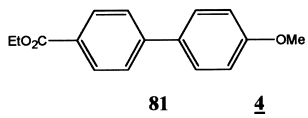
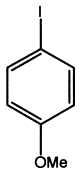
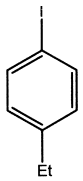
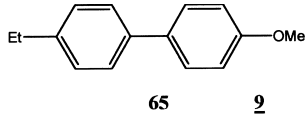
We have studied the effect of temperature (entries 1 and 7, Table 1). Yields are quite unchanged when electrolysis is performed at room temperature or at 50°C.

It appears that the yield of unsymmetrical compound dramatically increases with the amount of iodobenzene (2 equiv. vs. ArBr) (entries 1 and 10, Table 1).

We have also observed that the highest yields of unsymmetrical biaryl are obtained by applying an intensity of 0.2 A all along the electrolysis.

We have also tried to use 2,2′-bipyridine as ligand in the cross-coupling reaction. ArH is the major product formed, unlike what was observed with nickel catalysis.[17]

Table 3. Cross-coupling between two aryl iodides

Entry	ArI (10 mmol)	Ar′I (20 mmol)	Product, isolated yield (%) vs. initial ArI	ArH yield GC (%)	ArAr yield GC (%)	Ar′–Ar′/Ar′H
1			 **81** **4**	9	10	7.0
2			 **65** **9**	11	24	8.6

We have extended these results to the unsymmetrical coupling between various aryl iodides and bromides.

1.2. Cross-coupling of various aryl iodides with various aryl bromides

The general conditions corresponding to entry 10, Table 1 have been successfully applied to the cross-coupling of *ortho*, *meta* and *para* iodoanisoles with aryl bromides bearing electron-withdrawing groups. The results are reported in Table 2.

The yields seem not to depend on the position of the substituents either on the aryl iodide (entries 1–3, Table 2) or on the aryl bromide (entries 1 and 4, Table 2). Reaction has been also extended to aryl bromides bearing other electron-withdrawing groups. The corresponding biaryls were obtained in excellent yields (entries 4 and 5, Table 2).

We have studied the cross-coupling reaction between aryl iodides and aryl bromides both substituted by electron-withdrawing groups (entries 6 and 7, Table 2). Such products are not mentioned in the unsymmetrical coupling catalyzed by $Pd(OAc)_2$. In our process, 3 equiv. of aryl iodide are needed to lead to satisfactory yields.

Therefore, unsymmetrical biaryls both substituted by electron-withdrawing group are also accessible by our method, emphasizing the versatility of our electroreductive coupling process catalyzed by cobalt chloride in the acetonitrile/pyridine mixture (9:1). Supplementary examples of such unsymmetrical biaryls are presented in the following.

Obviously, the large excess of aryl iodide induces the formation of a large amount of the corresponding homocoupling biaryl Ar′–Ar′. In most cases, the presence of Ar′–Ar′, even as the major product in the medium, does not influence the extraction and purification of the unsymmetrical biaryl Ar–Ar′.

We have undertaken to replace aryl bromides by the corresponding iodides.

1.3. Cross-coupling between two aryl iodides

A good yield is observed for the coupling of ethyl 4-iodobenzene with 4-iodoanisole (entry 2, Table 3), which exhibit comparable reactivities towards electrogenerated Co^I. The yield increases with phenyl rings bearing electron-withdrawing group such as ethyl 4-iodobenzoate (entry 1, Table 3).

These results prompted us to undertake the study of the heterocoupling between two aryl bromides which are less expensive than the corresponding iodides.

1.4. Cross-coupling between two aryl bromides

We first studied the cross-coupling between aryl bromides alternatively substituted by an electron-donating group and by an electron-withdrawing group (entry 1, Table 4). Since the two aryls do not exhibit the same reactivity towards Co(I) species, a large excess of the more reactive one (3 equiv.) is introduced in the cell. Homocoupling biaryl product is also obtained in considerable amount. We have focused on the synthesis of unsymmetrical biaryls bearing two electron-withdrawing groups which are poorly described in one-step processes.

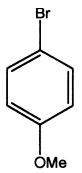
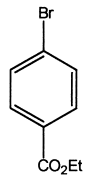
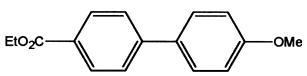
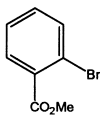
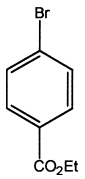
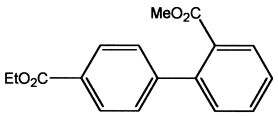
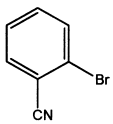
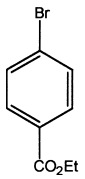
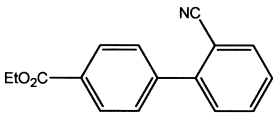
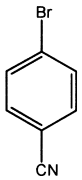
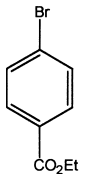
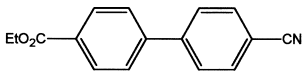
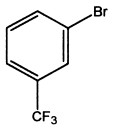
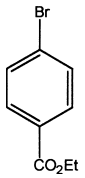
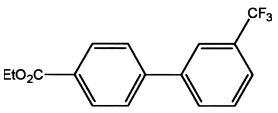
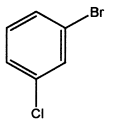
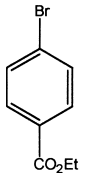
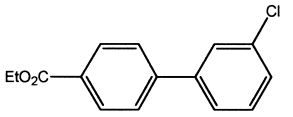
Several cross-coupling products are obtained in satisfactory yields (entries 2–4, Table 4). The yields become moderate if a less reactive aryl bromide is used (entries 5 and 6, Table 4) (no mesomer effect). With 3-bromobenzotrifluoride (entry 5, Table 4), the reduction product ArH is formed in larger amounts.

With 3-bromochlorobenzene (entry 6, Table 4), only the carbon–bromine bond is reactive. Experiments carried out between aryl bromides and aryl chlorides bearing electron-withdrawing group led to few unsymmetrical biaryl product. Besides, two different aryl chlorides may undergo cross-coupling reaction.

1.5. Cross-coupling between two aryl chlorides

Aryl chlorides must be substituted by electron-withdrawing group to be reactive[20] in this reaction catalyzed by cobalt salts. In that context, we have formed the unsymmetrical

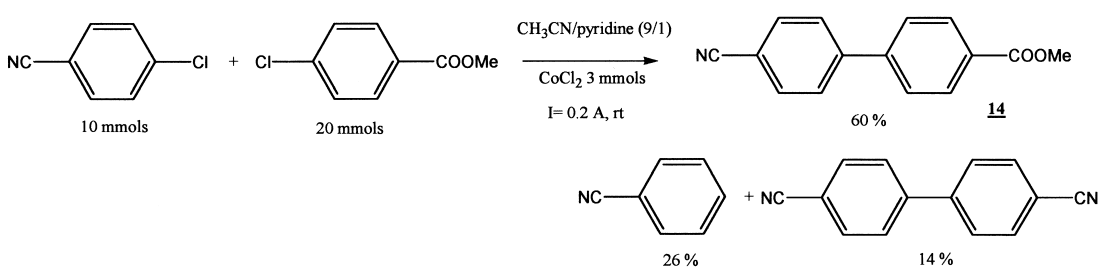
Table 4. Cross-coupling between two aryl bromides

Entry	ArBr (10 mmol)	Ar′Br (20 mmol)	Product, isolated yield (%) vs. initial ArBr	ArH yield GC (%)	ArAr yield GC (%)	Ar′–Ar′/Ar′H
1		 (30 mmol)	 **84** **4**	10	6	11
2			 **82** **10**	13	5	2.8
3			 **79** **11**	20	1	3.8
4			 **68** **12**	14	18	4.0
5			 **50** **7**	30	20	0.7
6			 **52** **13**	14	34	3.9

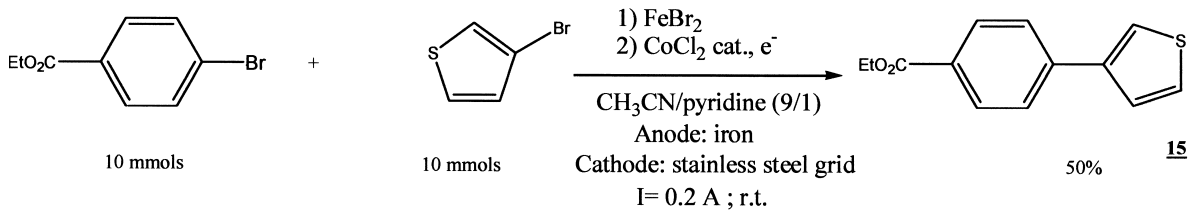
biaryl from 4-chlorobenzonitrile and methyl 4-chlorobenzoate in a correct yield. Reaction proceeds with lower rates in this case owing to their poor reactivity (Scheme 3).

1.6. Coupling between an aryl bromide and 3-bromothiophene

The good results obtained with two different aryl halides prompted us to examine the cross-coupling between an aromatic halide and a 3-halothiophene. These 3-arylthiophenes are of great interest in the synthesis of poly(3-substituted thiophenes) which are highly conducting polymers.[26] Previously, in our laboratory, we have shown that 3-arylthiophenes could be synthesized by coupling between 3-thienylzinc bromide and aromatic halides via a palladium catalysis.[27] However, this synthesis requires both



Scheme 3.



Scheme 4.

the preparation of the organozinc species from 3-bromothiophene (which is very difficult to obtain from non-electrochemical methods[28]) and the use of palladium catalysis for the cross-coupling. Therefore, we have undertaken to carry out the direct cross-coupling between an aromatic halide and 3-bromothiophene.

It comes out that the general conditions used in the previous examples do not apply to the preparation of 3-arylthiophene. As a matter of fact, the coupling product is obtained in 28% yield using two equivalents of ethyl 4-bromobenzoate, and the major product formed is thiophene (only a low proportion of ethyl 4-bromobenzoate reacts). Conversely, a 2 equiv. excess of 3-bromothiophene leads to the formation of 3,3′-bithiophene, which inhibits the cross-coupling reaction. The cobalt catalyst is most likely too strongly coordinated to the thiophene species, therefore becoming less efficient in the heterocoupling process.

We have recently discovered that the presence of iron salts at the beginning of the electrolysis could circumvent this problem. They are generated by oxidation of an iron anode along with the reduction of 1,2-dibromoethane prior to the introduction of the reagents, as described for the synthesis of 2-arylpyrimidines and 2-arylpyrazines.[19] Then, the presence of the iron anode allows the electrochemical coupling reaction to proceed efficiently for the arylation of 3-bromothiophene according to Scheme 4.

Under these conditions, an excess of either aryl or thienyl reagent gave less satisfactory yields. Therefore, we have extended the cross-coupling to different aryl bromides with 3-bromothiophene. Thirty-five percent of cross-coupling product (**16**) and 35% of symmetrical biaryl are obtained with 4-bromoacetophenone. With an aromatic bromide either unsubstituted or bearing an electron-donating group, the starting product is poorly consumed and therefore a low proportion of cross-coupling product is formed. No reaction occurs with aryl chloride substituted by an electron-withdrawing group.

Owing to these moderate results, we have not carried on that study any further.

2. Conclusion

We have developed a Co-catalyzed electrochemical process devoted to the preparation of unsymmetrically substituted biaryls from two different aryl halides. The coupling reaction is compatible with various electron-donating or withdrawing substituents. This procedure is also efficient with *ortho* substituted aromatic halides. This very versatile process compares favorably with the procedure described by Lemaire et al.[12] since the excess of the more reactive aromatic halide does not bring additional difficulties in the separation steps. Therefore, the isolated yields are good to excellent. To our knowledge, this is the first palladium-free direct preparation of unsymmetrical biaryls. Besides, the best results are obtained using an iron anode and work is now in progress to elucidate the role played by iron cations in the overall process.

3. Experimental

3.1. General procedure

The electrochemical cell was similar to that described previously.[29] The single compartment electrochemical cell was fitted by an iron rod as anode surrounded by a stainless steel grid cathode. In a mixture of acetonitrile (45 ml) and pyridine (5 ml) containing cobalt chloride (3 mmol) and tetrabutylammonium tetrafluoroborate (0.1 g), we introduce the less reactive aryl halide in amounts of 10 mmol and the more reactive one in excess (20 or 30 mmol). The solution was electrolyzed under argon at current constant intensity of 0.2 A at room temperature until two aryl halides wholly reacted. The solution was hydrolyzed with HCl (2N) and extracted with diethyl ether, the organic layer washed with brine, dried and the solvent evaporated under vacuum. Unsymmetrical products were isolated by column chromatography on silica gel with pentane/ether as eluent and were characterized by NMR (^{1}H, ^{13}C and ^{19}F), mass spectrometry and elemental analysis.

3.2. Product analysis

^{1}H (δ, ppm from TMS), ^{13}C (δ, ppm from TMS) and ^{19}F NMR (δ, ppm from $CFCl_3$) spectra were recorded on AC200 Bruker NMR spectrometer ($CDCl_3$ solution); mass spectra were measured on a Finnigan GC/MS ITD 800 spectrometer.

3.2.1. Biphenyl-4-carboxylic acid ethyl ester 1.[30] Yield: 75%; ^{1}H NMR (200 MHz) δ (ppm): 8.11 (dd, 2H, J=8.6, 1.8 Hz), 7.67–7.57 (m, 4H), 7.49–7.33 (m, 3H), 4.39 (q, CH_2, J=7.1 Hz), 1.40 (t, CH_3, J=7.1 Hz); ^{13}C NMR (50 MHz) δ (ppm): 166.5, 145.5, 140.0, 130.0, 129.2, 128.9, 128.1, 127.2, 127.0, 60.9, 14.3; MS, *m*/*z* (%): 227 (12) [M+1], 226 (78) [M$^+$], 198 (56), 182 (16), 181 (100), 153 (21), 152 (34).

3.2.2. 2′-Methoxy-biphenyl-4-carboxylic acid ethyl ester 2.[31] Yield: 85%; ^{1}H NMR (200 MHz) δ (ppm): 8.08 (dd, 2H, J=8.4, 1.7 Hz), 7.60 (dd, 2H, J=8.4, 1.7 Hz), 7.40–6.95 (m,

4H), 4.39 (q, CH_2, J=7.1 Hz), 3.81 (s, OMe), 1.40 (t, CH_3, J=7.1 Hz); ^{13}C NMR (50 MHz) δ (ppm): 166.3, 156.2, 143.1, 130.5, 129.1, 126.9, 120.7, 111.1, 60.6, 55.3, 14.2; MS, *m/z* (%): 257 (16) [M+1], 256 (99) [M$^+$], 228 (31), 212 (15), 211 (100), 183 (13), 169 (17), 168 (55), 139 (18).

3.2.3. 3′-Methoxy-biphenyl-4-carboxylic acid ethyl ester 3.[31] Yield: 72%; ^{1}H NMR (200 MHz) δ (ppm): 8.10 (dd, 2H, J=8.5, 1.8 Hz), 7.64 (dd, 2H, J=8.5, 1.8 Hz), 7.37–7.13 (m, 3H), 6.96–6.90 (m, 1H), 4.39 (q, CH_2, J=7.1 Hz), 3.86 (s, OMe), 1.41 (t, CH_3, J=7.1 Hz); ^{13}C NMR (50 MHz) δ (ppm): 166.3, 159.9, 145.2, 141.4, 129.8, 129.2, 126.9, 119.6, 113.3, 112.9, 60.8, 55.2, 14.2; MS, *m/z* (%): 257 (17) [M+1], 256 (96) [M$^+$], 228 (53), 212 (21), 211 (100), 183 (12), 168 (28), 153 (15), 152 (12), 140 (12), 139 (16).

3.2.4. 4′-Methoxy-biphenyl-4-carboxylic acid ethyl ester 4.[32] Yield: 88%; ^{1}H NMR (200 MHz) δ (ppm): 8.08 (d, 2H, J=8.4 Hz), 7.61 (d, 2H, J=8.4 Hz), 7.57 (d, 2H, J=8.8 Hz), 6.98 (d, 2H, J=8.8 Hz), 4.39 (q, CH_2, J=7.1 Hz), 3.85 (s, OMe), 1.41 (t, CH_3, J=7.1 Hz); ^{13}C NMR (50 MHz) δ (ppm): 166.3, 159.6, 144.9, 132.2, 129.8, 128.1, 126.2, 114.1, 60.7, 55.1, 14.1; MS, *m/z* (%): 257 (22) [M+1], 256 (100) [M$^+$], 228 (54), 211 (76), 168 (26).

3.2.5. 2′-Methoxy-biphenyl-2-carboxylic acid methyl ester 5.[33] Yield: 90%; ^{1}H NMR (200 MHz) δ (ppm): 7.89 (d, 1H, J=8.2 Hz), 7.55–6.86 (m, 7H), 3.66 (s, 3H, COOMe), 3.63 (s, 3H, OMe); ^{13}C NMR (50 MHz) δ (ppm): 168.5, 156.1, 138.9, 131.5, 131.2, 130.4, 129.8, 129.2, 128.7, 126.9, 120.8, 110.2, 55.1, 51.5; MS, *m/z* (%): 242 (34) [M$^+$], 211 (100), 196 (39), 168 (24), 149 (22).

3.2.6. 4′-Methoxy-biphenyl-2-carbonitrile 6.[34] Yield: 81%; ^{1}H NMR (200 MHz) δ (ppm): 7.75–6.91 (m, 8H), 3.84 (s, 3H, OMe); ^{13}C NMR (50 MHz) δ (ppm): 160.0, 145.2, 133.7, 132.7, 130.5, 130.0, 129.9, 127.0, 119.0, 114.1, 111.0, 55.2; MS, *m/z* (%): 210 (16) [M+1], 209 (100) [M$^+$], 194 (37), 180 (12), 179 (10), 167 (11), 166 (70), 140 (20), 139 (13).

3.2.7. 3′-Trifluoromethyl-biphenyl-4-carboxylic acid ethyl ester 7.[30] Yield: 57%; ^{1}H NMR (200 MHz) δ (ppm): 8.17–8.11 (m, 2H), 7.85–7.53 (m, 6H), 4.41 (q, CH_2, J=7.1 Hz), 1.42 (t, CH_3, J=7.1 Hz); ^{13}C NMR (50 MHz) δ (ppm): 166.1, 143.7, 140.7, 131.4 (q, J=32.5 Hz), 130.4, 130.1, 129.2, 126.9, 124.6, 124.0 (q, J=272.4 Hz), 60.9, 14.1; ^{19}F NMR (50 MHz) δ (ppm): −62.5 (3F, s); MS, *m/z* (%): 294 (57) [M$^+$], 266 (59), 250 (17), 249 (100), 201 (32), 152 (17).

3.2.8. 3′-Trifluoromethyl-biphenyl-2-carbonitrile 8. Yield: 81%; ^{1}H NMR (200 MHz) δ (ppm): 7.79–7.41 (m, 8H); ^{13}C NMR (50 MHz) δ (ppm): 143.8, 139.0, 133.9, 133.2, 132.2, 131.2 (q, J=32.6 Hz), 130.1, 129.4, 128.4, 125.5, 124.0 (q, J=272.4 Hz), 118.3, 111.4; ^{19}F NMR (50 MHz) δ (ppm): −62.3 (3F, s); MS, *m/z* (%): 248 (15) [M+1], 247 (100) [M$^+$], 228 (10), 227 (23), 226 (15), 208 (13), 182 (15), 177 (11). Anal. calcd for $C_{14}H_8F_3N$: C, 68.02; H, 3.26; N, 5.67. Found: C, 67.90; H, 3.43; N, 5.79.

3.2.9. 4′-Ethyl-4-methoxy-biphenyl 9.[35] Yield: 65%; ^{1}H NMR (200 MHz) δ (ppm): 7.53–7.44 (m, 4H), 7.23 (d, 2H, J=8.2 Hz), 6.94 (dd, 2H, J=8.8, 1.9 Hz), 3.80 (s, 3H, OMe), 2.66 (q, CH_2, J=7.6 Hz), 1.25 (t, CH_3, J=7.6 Hz); ^{13}C NMR (50 MHz) δ (ppm): 159.0, 142.8, 138.3, 133.8, 128.3, 128.1, 126.7, 114.2, 55.4, 28.6, 15.7; MS, *m/z* (%): 212 (68) [M$^+$], 198 (14), 197 (100), 182 (13), 154 (22).

3.2.10. Biphenyl-2,4′-dicarboxylic acid 4′-ethyl ester 2-methyl ester 10.[36] Yield: 82%; ^{1}H NMR (200 MHz) δ (ppm): 8.20–7.36 (m, 8H), 4.42 (q, CH_2, J=7.1 Hz), 3.68 (s, COOMe) 1.44 (t, CH_3, J=7.1 Hz); ^{13}C NMR (50 MHz) δ (ppm): 168.4, 166.3, 145.9, 141.5, 131.4, 130.4, 130.0, 129.1, 128.2, 127.7, 127.0, 60.8, 51.9, 14.2; MS, *m/z* (%): 284 (99) [M$^+$], 256 (41), 253 (22), 239 (100), 225 (31), 181 (70), 152 (23).

3.2.11. 2′-Cyano-biphenyl-4-carboxylic acid ethyl ester 11. Yield: 79%; ^{1}H NMR (200 MHz) δ (ppm): 8.09 (dd, 2H, J=8.3, 1.8 Hz), 7.73–7.37 (m, 6H), 4.42 (q, CH_2, J=7.1 Hz), 1.42 (t, CH_3, J=7.1 Hz); ^{13}C NMR (50 MHz) δ (ppm): 166.1, 144.3, 142.3, 132.9, 130.7, 130.0, 128.2, 118.2, 111.3, 61.1, 14.4; MS, *m/z* (%): 251 (38) [M$^+$], 228 (13), 223 (91), 207 (18), 206 (100), 179 (47), 178 (42), 177 (20), 151 (44), 150 (22). Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.45; H, 5.18; N, 5.63.

3.2.12. 4′-Cyano-biphenyl-4-carboxylic acid ethyl ester 12.[37] Yield: 68%; ^{1}H NMR (200 MHz) δ (ppm): 8.14 (dd, 2H, J=8.5, 1.6 Hz), 7.77–7.63 (m, 6H), 4.23 (q, CH_2, J=7.1 Hz), 1.42 (t, CH_3, J=7.1 Hz); ^{13}C NMR (50 MHz) δ (ppm): 165.9, 144.2, 143.1, 132.5, 130.4, 130.1, 127.7, 127.0, 118.5, 111.6, 61.0, 14.2; MS, *m/z* (%): 251 (46) [M$^+$], 223 (66), 206 (100), 178 (27), 177 (22), 151 (35).

3.2.13. 3′-Chloro-biphenyl-4-carboxylic acid ethyl ester 13. Yield: 52%; ^{1}H NMR (200 MHz) δ (ppm): 7.95 (dd, 2H, J=8.4, 1.7 Hz), 7.44 (dd, 2H, J=8.4, 1.7 Hz), 7.34–7.17 (m, 4H), 4.26 (q, CH_2, J=7.1 Hz), 1.27 (t, CH_3, J=7.1 Hz); ^{13}C NMR (50 MHz) δ (ppm): 166.1, 143.7, 141.6, 134.7, 130.0, 129.7, 127.9, 127.2, 127.1, 126.9, 125.2, 60.9, 14.1; MS, *m/z* (%): 262 (23) [M$^+$], 260 (69) [M$^+$], 234 (18), 232 (67), 217 (35), 216 (15), 215 (97), 153 (14), 152 (100), 151 (13). Anal. calcd for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03. Found: C, 69.84; H, 5.23.

3.2.14. 4′-Cyano-biphenyl-4-carboxylic acid methyl ester 14.[38] Yield: 60%; ^{1}H NMR (200 MHz) δ (ppm): 8.14 (dd, 2H, J=8.3, 1.7 Hz), 7.78–7.63 (m, 6H), 3.95 (s, COOMe); ^{13}C NMR (50 MHz) δ (ppm): 166.6, 144.4, 143.4, 132.7, 130.2, 127.9, 127.2, 118.7, 111.8, 52.3; MS, *m/z* (%): 237 (64) [M$^+$], 207 (13), 206 (100), 178 (27), 177 (17), 151 (32).

3.2.15. 4-Thiophen-3-yl-benzoic acid ethyl ester 15.[39] Yield: 50%; ^{1}H NMR (200 MHz) δ (ppm): 7.96 (d, 2H, J=8.4 Hz), 7.57 (d, 2H, J=8.4 Hz), 7.44 (dd, 1H, J=4.0, 2.0 Hz), 7.27 (m, 2H), 4.29 (q, CH_2, J=7.1 Hz), 1.30 (t, CH_3, J=7.1 Hz); ^{13}C NMR (50 MHz) δ (ppm): 166.4, 141.2, 139.9, 130.1, 128.9, 126.6, 126.1, 121.8, 60.9, 14.3; MS, *m/z* (%): 233 (17) [M+1], 232 (100) [M$^+$], 205 (15), 204 (38), 187 (72), 159 (11), 115 (22).

3.2.16. 1-(4-Thiophen-3-yl-phenyl)-ethanone 16.[39] Yield: 35%; ^{1}H NMR (200 MHz) δ (ppm): 8.00 (m, 2H), 7.68 (m, 2H), 7.58 (m, 1H), 7.44 (m, 2H), 2.62 (s, CH_3); ^{13}C NMR

(50 MHz) δ (ppm): 197.5, 141.1, 140.2, 135.6, 129.0, 126.7, 126.2, 122.0, 26.5; MS, *m*/*z* (%): 202 (64) [M^+], 188 (12), 187 (100), 159 (24), 115 (43).

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